# Resveratrol

# VALORISATION

## Societal Relevance

Obesity, cardiovascular diseases and Type 2 Diabetes (T2D) are tightly linked to our modern lifestyle, which is characterised by overconsumption of food and a lack of physical activity [1]. Currently, these so called non-communicable diseases are the leading cause of death worldwide. It is therefore of utmost importance that effective preventive and curative treatments are being developed for this class of diseases. T2D is characterised by a decreased sensitivity to the hormone insulin, leading to a dysregulation of glucose metabolism [2]. On the long-term high blood glucose levels can give complications such as a stroke, heart disease, kidney failure and blindness [3]. Existing strategies that promote a healthy diet and stimulate physical activity are effective but have been shown to be challenging to adhere to for most people. Therefore, it is important to explore other treatment options for cardiovascular diseases and T2D that are easier to adhere to.

Over the years, the interest in red wine has steadily increased. There is much debate about whether red wine has beneficial health effects or not. This debate originates from the late 1980s when an apparently paradoxical epidemiological observation was made in French people: they had a relatively low incidence of coronary heart disease while having a diet rich in saturated fats [4]. Since the publication of this epidemiological observation, research aimed at identifying which compound was responsible for these so-claimed beneficial health effects. In 2003, was discovered that the polyphenol resveratrol – present in red wine - could activate sirtuin 1 (SIRT1) [5]. SIRT1 is an important regulator in cellular energy homeostasis and its activity is linked to longevity [6], thereby making resveratrol an interesting candidate for further research and was marked as a potential player in the French paradox. Even though soon it became clear that the amounts of resveratrol in red wine are too low to explain health effects of red wine – and the French paradox has been suggested to be an illusion – animal studies with resveratrol presented promising results.

The aim of this dissertation was to investigate if the food supplement *trans*-resveratrol can be used in prevention of T2D or can be used as a supportive tool in the management of T2D in humans. Three human clinical trials have been performed, that were specifically designed to provide evidence that resveratrol can help in prevention and treatment of T2D, by improving insulin sensitivity, mitochondrial function and liver fat accumulation. Unfortunately, despite robust improvements in mitochondrial function, resveratrol supplementation for a period of 30 days did not improve insulin sensitivity and liver fat accumulation. Nevertheless, when resveratrol is supplied for a longer period this might be beneficial for prevention of T2D, since for example a decrease in HbA1c was seen when resveratrol was supplied for six months. HbA1c is a marker of long-term glucose homeostasis, and thereby an important biomarker for the onset of T2D.

Therefore, these results are promising and indicate that resveratrol supplementation might still be beneficial in the prevention and treatment of metabolic disturbances - such as T2D - when supplied for a longer period.

### Economic Relevance

Novel, easy to adhere to, interventions that can prevent or treat T2D can have an enormous impact on the costs of health care. T2D embodies a major economic burden on health care systems since it is one of the most costly health problems [7]. According to the Dutch Government, the costs for diabetes care were 1.7 billion euro in 2011 in just The Netherlands [8]. Ever since, the number of people suffering from diabetes has only increased and thereby the health costs as well. Thus, food supplements can be an inexpensive and easy supportive tool to prevent and treat T2D, which could scale down the medical costs significantly.

### Translation into Practice

Even though in the 30-day clinical trials described in this dissertation we did not see effects on insulin sensitivity, this does not mean we did not make important progress in this field of research. A very important finding is that we saw a robust improvement in mitochondrial function in both patients with T2D and men at increased risk of T2D. Since mitochondrial dysfunction is linked to insulin resistance and metabolic diseases, achieving an improvement in mitochondrial function by just using a food supplement is astonishingly and promising. It should be explored further if the treatment duration of 30-days might have been too short, or if resveratrol supplementation should be combined with a physical activity program to achieve beneficial effects on whole body energy metabolism.

Furthermore, the results presented in this dissertation are or will be used for original scientific articles. These articles have been published in or will be submitted to international well-known peer-reviewed journals. Thereby, the knowledge is shared that can be acquired from these studies with scientists worldwide. In addition, the data from the different studies has also been presented at several national and international conferences and symposia which also helps to increase visibility of the results and thereby could contribute to new insights and ideas for future research.



### Planning and Realisation

Supplementation for 30-days with resveratrol in patients with T2D and men at increases risk significantly increased mitochondrial function but did not improve insulin sensitivity or other markers related to metabolic health. An interim-analyses of a long-term study with resveratrol indicated that the treatment duration of 30-days might have been too short to elicit beneficial effects on whole body energy metabolism. Completion of this long-term study will help to answer the question if resveratrol is a promising candidate to improve metabolic health in

humans or not. Furthermore, it became apparent that resveratrol seems to be beneficial in certain individuals but not in others. Differences in participant characteristics could play a role herein, for example the serum bilirubin levels seem to be predictive for response to resveratrol. This relationship has not been observed before and should be explored further, to be able to identify for who resveratrol might still be useful for promoting health. The latter also matches the increasing call for so-called personalised medicine, which is based on the principle of dividing patients into different groups, with medical decisions, practices, interventions and/or products being tailored to the patient based on their predicted response or risk of disease [9]. The focus on individualisation, by personalised medicine, can have economic benefits as well as limit the expenditure on treatments to just the population who are most likely to benefit, thus saving health care costs [9]. Underlining the importance to explore the role of bilirubin - and potentially also other participants characteristics - in the effectiveness of resveratrol.

To achieve these goals, the long-term resveratrol study will be finalised– to see if resveratrol supplementation does have beneficial effects beyond improving mitochondrial function when supplied for a longer period - and extra analysis will be performed related to bilirubin metabolism to shed light on the relationship between serum bilirubin levels and effectiveness of resveratrol.

## REFERENCES


1. Collaboration, N.C.D.R.F., *Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults*. Lancet, 2017. **390**(10113): p. 2627-2642.
2. Virally, M., et al., *Type 2 diabetes mellitus: epidemiology, pathophysiology, unmet needs and therapeutical perspectives*. Diabetes Metab, 2007. **33**(4): p. 231-44.
3. Warram, J.H., et al., *Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents.* Ann Intern Med, 1990. **113**(12): p. 909-15.
4. Renaud, S. and M. de Lorgeril, *Wine, alcohol, platelets, and the French paradox for coronary heart disease.* Lancet, 1992. **339**(8808): p. 1523-6.
5. Howitz, K.T., et al., *Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan.* Nature, 2003. **425**(6954): p. 191-6.
6. Canto, C. and J. Auwerx, *Caloric restriction, SIRT1 and longevity.* Trends Endocrinol Metab, 2009. **20**(7): p. 325-31.
7. American Diabetes, A., *Economic Costs of Diabetes in the U.S. in 2017.* Diabetes Care, 2018. **41**(5): p. 917-928.
8. RIVM, *Kosten van Ziekten database 2013*. 2013.
9. Maughan, T., *The Promise and the Hype of 'Personalised Medicine'.* New Bioeth, 2017. **23**(1): p. 13-20.